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10/674,387	10/01/2003	Yoshihide Iwaki	2870-0266P	4434

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
10/19/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/674,387	IWAKI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4 and 11-26* is/are pending in the application.

4a) Of the above claim(s) *12-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,11,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-4 and 11-26 are pending.
Claims 1 and 5-10 are cancelled.
Claims 12-24 are withdrawn.
Claims 2-4, 11, 25, and 26 are examined on the merits.

1. This Office Action is in reply to Applicants' correspondence of 07/27/2007.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance.

The Office Action contains new grounds of rejection that are necessitated by Applicant's amendments to the claims. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

2. Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Claim Rejections - 35 USC § 112

3. The rejection of claim 26 under 35 USC 112 2nd as indefinite, as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendment to claim 26.

Withdrawn Claim Rejections - 35 USC § 102

4. the rejection of slaims 2, 5, 6, 7, 11 and 25 under 35 U.S.C. 102(b) as being anticipated by Ye et al (2001) is **WITHDRAWN** in light of the amendments to independent claim 25, which incorporates the subject matter of claims 8, 9, and 10.

5. The rejection of claims 2-7, 11 and 25 under 35 U.S.C. 102(b) as being anticipated by Ferrie et al (1992) is **WITHDRAWN** in light of the amendments to independent claim 25, which incorporates the subject matter of claims 8, 9, and 10.

Maintained Claim Rejections - 35 USC § 103

4. Claims 2, 11, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ye et al (2001) in view of Durward et al (1998) and Fujisaki at al (1999) US Patent 5,935,520.

Ye et al teaches methods for detecting single nucleotide polymorphisms comprising designing allele specific primers wherein each primer has a different artificial mismatch nucleotide, and amplifying a sample with the primers. Ye et al shows that the amount of an amplification product from each primer is substantially the same when both alleles are present in the sample.

Regarding claim 25 (claim 25 is the independent claim, and thus discussed first in this rejection), Ye et al teaches designing two allele specific primers (Fig 1; and for example Table 2 -TNF -308G→A primers for A and G alleles). Specifically, Ye et al teaches a first primer (Table 2 Forward inner primer (A allele)) that contains an artificial mismatch (see Table 1, Tetra-primer ARMS-PCR primers have an additional mismatch at position -2 form the 3' terminus) and a nucleotide complementary to a first allele (see Table 1, Tetra-primer ARMS-PCR primers have an allele-specific mismatch at the 3' terminus). Ye et al further teaches a second primer (Table 2 Reverse inner primer (G allele)) that contains an artificial mismatch (see Table 1, Tetra-primer ARMS-PCR

primers have an additional mismatch at position -2 form the 3' terminus) and a nucleotide complementary to a second allele (see Table 1, Tetra-primer ARMS-PCR primers have an allele-specific mismatch at the 3' terminus). As such the two primers can distinguish between the two alleles. The artificial mismatch nucleotides in the first and second primers are different (G and A in the first and second primers, respectively). Ye et al further teaches amplifying a sample with the recited primers (p.3 – Tetra-primer ARMS-PCR) and shows that the amount of amplification product from each primer is substantially the same in a heterozygous sample, where both alleles are present in the sample (Fig 2A, top picture, lane 2 for example).

Regarding claim 2, Ye et al teaches that the Allele-specific mismatch is at the 3'-terminal base (Table 1), thus the primers have a polymorphic site within 4 nucleotides from the 3'terminus of the allele-specific primers.

Regarding claim 11, Ye et al teaches determining the presence of each allele, thus determining the homo/heterozygosity of the SNP (Fig 2).

Ye et al does not teach the analysis of a PCR by-product that is pyrophosphoric acid (PPi) for detection, relevant to the requirements of claim 25.

Durward et al teaches a colorimetric method for detecting amplified nucleic acids based on measuring PPi (p.608, right col., lns.23-28). The reference teaches that during the PCR reaction the incorporation of dNMPs from dNTPs into amplified nucleic acids generates inorganic pyrophosphate (PPi, pyrophosphoric acid) in a predicatable 1:1 molar ratio (p.608, right col., lns.18-28; Fig.1). The reference further teaches that PPi can be hydrolyzed to inorganic phosphate (Pi) (p.608, right col., ln.s.31-32), that

detection and measurement of Pi is a measure of PCR performance (p.608, right col., lns.33-36), and describe an assay for Pi measurement (p.608, right col., lns.41-52). Durward also provides examples in which amplified DNA is detected by Pi measurement (Fig.2; Fig.3; Table 1). Because the Pi results directly from the hydrolysis of PPi, this measuring technique is using the PPi.

Neither Ye et al or Durward et al teaches the use of a dry analytical element for the analysis of production of the PCR product, relevant to the requirements of claim 25.

Fujisaki et al teaches a dry analytical element for analyzing an analyte in a sample solution using a colorimetric reaction (col.1. lns.39-50). The reference teaches the use of a reagent layer in the element that contains components necessary for producing a colorimetric reaction.

Ye et al does not provide primers in which the two different mismatched nucleotides are adenine in a first primer and cytosine in a second primer, relevant to claim 26.

However, Ye does teach a rationale for providing a mismatched nucleotide in a primer (p.2, right col., lns.3-11). Ye et al teaches that different mismatches can be either 'strong' (G/A or C/T mismatches), 'weak' (C/A or G/T mismatches), or 'medium' (A/A, C/C, G/G, or T/T mismatches), and that one can pair the mismatches within a primer to achieve the desired level of selectivity.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the allele specific amplification methods of Ye et al with the phosphate measurement detection methods of Durward et al. One would

have been motivated to do so based on the assertion of Durward et al that PCR measurement by phosphate detection can offer advantages in terms of speed and low cost (p.610, left col., lns.35-36). One would have had a reasonable expectation of success because Durward et al provides examples of sensitive and specific detection of PCR performance using the method (Fig.2; Fig.3). It would further have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Durward et al to have included the dry analytical element taught by Fujisaki et al for the measurement of PCR performance. One would have been motivated to do so based upon the assertion of Fujisaki et al that such dry analytical elements provide for the simple and rapid analysis of sample solutions (col.1 lns.32-37). One would have had a reasonable expectation of success in combining the methods of Durward et al and Fujisaki et al because Fujisaki et al teaches that dry analytical elements can utilize color reaction based assays (col. 1 lns.45-50) in which components necessary for the coloring reaction are contained in a reagent layer (col 8 lns.45-47), and Durward et al demonstrate that the reagents used to create the color change (molybdate and Fiske-Subbadow solution) to measure PCR performance are added sequentially to the PCR mix for the assay (p.609, middle col., lns.10-18).

Regarding the limitations of claim 26, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the general method taught by Ye et al so as to have used any mismatched nucleotides, including an adenine in a first primer and a cytosine in a second primer, that would provide the desired level of amplification selectivity for each primer. Such

experimentation to provide different oligonucleotide primers with different artificial mismatches would be routine to one of skill in the art at the time the invention was made, as evidenced by the teachings and examples of Ye et al.

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

Response to Remarks

Applicants have traversed the rejection of claims uncer 35 USC 103 as obvious in view of the teachings of Ye et al, Durward et al, and Fujisaki et al. Applicants have argued (p.10-11) that the method of independent claim 25 is carried out by measuring pyrophosphoric acid in a dry analytical element without performing electrophoresis, and that such methodology has advantages as compared with an electrophoresis-based analysis as taught by Ye et al. Applicants argue that an analysis using a dry analytical element to measure pyrophosphoric acid is quantitative, fast, convenient, and avoids some harmful reagents such as intercalators. Applicants' argument is not found to be persuasive. Such advantages of dry analytical element-based methods are not particularly unexpected, and were known in the art at the time the invention was made; for example, Fujisaki et al specifically teach that dry analytical elements provide for the simple and rapid analysis of sample solutions (col.1 lns.32-37), and teaches the quantitative nature of method using dry analytical elements (col.1 lns.15-22). Additionally, it is noted that the claims are examined on the basis of what they recite and thus require, therefore an advantage or benefit of the invention is not given

consideration unless it is specifically recited in and required by the limitations of the claim.

The rejection as set forth is **MANTAINED**

New Claim Rejections - 35 USC § 103

5. Claims 2-4, 11, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrie et al (1992) in view of Durward et al (1998) and Fujisaki at al (1999) US Patent 5,935,520.

Ferrie et al teaches a method for the analysis of mutations in the CFTR gene, including single nucleotide polymorphisms. Ferrie et al teaches designing and allele specific primers wherein each primer has a different artificial mismatch nucleotide (Table 4 - 621 +1G>T), and amplifying a sample with the primers. Ferrie et al shows that the amount of an amplification product from each primer is substantially the same when both alleles are present in the sample.

Regarding claim 25 (claim 25 is the independent claim, and thus discussed first in this rejection), Ferrie et al teaches designing two allele specific primers (Table 3 – ΔF508 primers DF-j-N and DF-w-M; Fig 1). It is noted that while the F508 mutation is fully described as a deletion of 3 nucleotides, the primers of Ferrie et al can be considered as detecting a single nucleotide polymorphism (i.e. the primers detect whether the nucleotide prior to the sequence context TTGGTGTT (in Fig 1 a)) is either a 'T' (normal sequence) or an 'A' (F508 sequence). Specifically, Ferrie et al teaches a first primer (Table 3 DF-j-N primer) that contains an artificial mismatch (see Figure 1 a)

and a nucleotide complementary to a first allele (the primer has a 3'-terminal A complementary to the 'normal' allele). Ferrie et al further teaches a second primer (Table 3 DF-w-M primer) that contains an artificial mismatch and a nucleotide complementary to a second allele (the primer has a 3'-terminal T complementary to the 'F508' allele). As such the two primers can distinguish between the two alleles. The artificial mismatch nucleotides in the first and second primers are different (C and T in the first and second primers, respectively). Ferrie et al further teaches amplifying a sample with the recited primers (Figure 1a) and shows that the amount of amplification product from each primer is substantially the same in a heterozygous sample, where both alleles are present in the sample (Fig 1a), gel picture, lanes in sample 4 for example.

Regarding claim 2, Ferrie et al teaches primers in which the allele-specific mismatch is at the 3'-terminal base (Figure 1a)), thus the primers have a polymorphic site within 4 nucleotides from the 3'terminus of the allele-specific primers.

Regarding claims 3 and 4, the reference teaches that the artificial mismatch nucleotide is adjacent to the allele-specific nucleotide in each primer (Fig 1a)), thus teaching that the mismatch nucleotide is introduced to the nucleotide adjacent to the polymorphic site in at least one (relevant to claim 3) and both (relevant to claim 3) primers.

Regarding claim 11, Ferrie et al teaches determining the presence of each allele, thus determining the homo/heterozygosity of the polymorphic position (Fig 1a) teaches

analysis of normal samples (homozygous for no F508 deletion) and ΔF508 heterozygous sample).

Ferrie et al does not teach a method in which a pyrophosphoirc acid, as a by-product of polymerase reactions, is detected using a dry analytical reagent, as required by claim 25.

Durward et al teaches a colorimetric method for detecting amplified nucleic acids based on measuring PPi (p.608, right col., lns.23-28). The reference teaches that during the PCR reaction the incorporation of dNMPs from dNTPs into amplified nucleic acids generates inorganic pyrophosphate (PPi, pyrophosphoric acid) in a predicatable 1:1 molar ratio (p.608, right col., lns.18-28; Fig.1). The reference further teaches that PPi can be hydrolyzed to inorganic phosphate (Pi) (p.608, right col., ln.s.31-32), that detection and measurement of Pi is a measure of PCR performance (p.608, right col., lns.33-36), and describe an assay for Pi measurement (p.608, right col., lns.41-52). Durward also provides examples in which amplified DNA is detected by Pi measurement (Fig.2; Fig.3; Table 1). Because the Pi results directly from the hydrolysis of PPi, this measuring technique is using the PPi.

Neither Ferrie et al or Durward et al teaches the use of a dry analytical element for the analysis of production of the PCR product, relevant to the requirements of claim 25.

Fujisaki et al teaches a dry analytical element for analyzing an analyte in a sample solution using a colorimetric reaction (col.1. lns.39-50). The reference teaches

the use of a reagent layer in the element that contains components necessary for producing a colorimetric reaction.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the allele specific amplification methods of Ferrie et al with the phosphate measurement detection methods of Durward et al. One would have been motivated to do so based on the assertion of Durward et al that PCR measurement by phosphate detection can offer advantages in terms of speed and low cost (p.610, left col., lns.35-36). One would have had a reasonable expectation of success because Durward et al provides examples of sensitive and specific detection of PCR performance using the method (Fig.2; Fig.3). It would further have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Durward et al to have included the dry analytical element taught by Fujisaki et al for the measurement of PCR performance. One would have been motivated to do so based upon the assertion of Fujisaki et al that such dry analytical elements provide for the simple and rapid analysis of sample solutions (col.1 lns.32-37). One would have had a reasonable expectation of success in combining the methods of Durward et al and Fujisaki et al because Fujisaki et al teaches that dry analytical elements can utilize color reaction based assays (col. 1 lns.45-50) in which components necessary for the coloring reaction are contained in a reagent layer (col 8 lns.45-47), and Durward et al demonstrate that the reagents used to create the color change (molybdate and Fiske-Subbadow solution) to measure PCR performance are added sequentially to the PCR mix for the assay (p.609, middle col., lns.10-18).

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

Conclusion

No claim is allowable. No claim is free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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